### **PATENT COOPERATION TREATY**

From the INTERNATIONAL SEARCHING AUTH	ORITY	·	REC'D 1 8 AUG 2005				
То:			PCT PCT				
see form PCT/ISA/220		WRITTEN OPINION OF THE INTERNATIONAL SEARCHING AUTHORITY (PCT Rule 43bis.1)					
		Date of mailing (day/month/year) se	e form PCT/ISA/210 (second sheet)				
Applicant's or agent's file reference see form PCT/ISA/220		FOR FURTHER A See paragraph 2 belo					
International application No. PCT/EP2005/000562	International filing date (c 18.01.2005	day/month/year)	Priority date (day/month/year) 22.01.2004				
International Patent Classification (IPC) or both national classification and IPC C07K14/195, C12N15/31, C07K16/12, C12Q1/68, A61K39/02							
Applicant AKZO NOBEL N.V.	·						
<ul> <li>☑ Box No. I Basis of the op</li> <li>☐ Box No. II Priority</li> <li>☐ Box No. III Non-establishn</li> <li>☑ Box No. IV Lack of unity of</li> <li>☑ Box No. V Reasoned state applicability; cit</li> <li>☐ Box No. VI Certain document</li> <li>☐ Box No. VII Certain defects</li> <li>☐ Box No. VIII Certain observent</li> <li>2. FURTHER ACTION</li> </ul>	Box No. I Basis of the opinion  □ Box No. II Priority □ Box No. III Non-establishment of opinion with regard to novelty, inventive step and industrial applicability □ Box No. IV Lack of unity of invention □ Box No. V Reasoned statement under Rule 43bis.1(a)(i) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement □ Box No. VI Certain documents cited □ Box No. VII Certain defects in the international application □ Box No. VIII Certain observations on the international application  FURTHER ACTION						
written opinion of the International Preliminary Examining Authority ("IPEA"). However, this does not apply where the applicant chooses an Authority other than this one to be the IPEA and the chosen IPEA has notifed the International Bureau under Rule 66.1 bis(b) that written opinions of this International Searching Authority will not be so considered.							
submit to the IPEA a written reply months from the date of mailing of whichever expires later.							
For further options, see Form PC		•					
3. For further details, see notes to F	orm PCT/ISA/220.						
Name and mailing address of the ISA:		Authorized Officer					

Name and mailing address of the ISA

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Hix, R

Telephone No. +31 70 340-3898



International application No. PCT/EP2005/000562

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	Box	( No. 1	Basis of the opinion	
1.	With the	tional application in		
		langua	ppinion has been established on the basis of a translation from the original language , which is the language of a translation furnished for the purposes of interer Rules 12.3 and 23.1(b)).	age into the following national search
2.	With nece	n regare essary	d to any <b>nucleotide and/or amino acid sequence</b> disclosed in the international to the claimed invention, this opinion has been established on the basis of:	application and
	a. ty	pe of r	material:	
	Σ	∄ as	sequence listing	
	C	J tab	ole(s) related to the sequence listing	
	b. fo	rmat o	f material:	•
	×	ın v	written format	
٠.	×	3 in c	computer readable form	
	c. tin	ne of fi	iling/furnishing:	
	×	a con	ntained in the international application as filed.	
	×	d filed	d together with the international application in computer readable form.	,
		] fum	nished subsequently to this Authority for the purposes of search.	
3.	!	has be copies	ition, in the case that more than one version or copy of a sequence listing and/or sen filed or furnished, the required statements that the information in the subseques is identical to that in the application as filed or does not go beyond the application or late, were furnished.	ent or additional
4.	Addit	tional c	comments:	

International application No. PCT/EP2005/000562

_	Po	x No. IV	Lack of unity o	finyontio	<u> </u>				
-									
1.		In resp	onse to the invitati	on (Form I	PCT/ISA/20	06) to pay additional fees, the applicant has:			
			paid additional fee	es.					
			paid additional fee	es under p	rotest.				
			not paid additiona	l fees.		·			
					,				
2.		This Au	uthority found that to clicant to pay additi	he require onal fees.	ment of u	nity of invention is not complied with and chose not to invite			
3.	Thi	s Author	ity considers that the	he require	ment of un	nity of invention in accordance with Rule 13.1, 13.2 and 13.3 i			
		complied	d with						
	×	not com	plied with for the fo	llowing rea	asons:				
		see separate sheet							
4.	Consequently, this report has been established in respect of the following parts of the international application:								
		all parts.							
	<b>×</b> 1	the parts	relating to claims	Nos. 1, 10	-14, 23-32	2			
		•	<b>G</b> ,	•					
_	Pos	k No. V	Poppanod state	mont und	lor Bulo 4	3bis.1(a)(i) with regard to novelty, Inventive step or			
	ind	ustrial a	pplicability; citati	ons and	explanation	ons supporting such statement			
1.	Sta	tement	•		-				
	Nov	· /elty (N)		Yes:	Claims	1, 10-14, 23-32			
		( ,	. •	No:	Claims				
	Inve	entive st	ep (IS)	Yes:	Claims	•			
				No:	Claims	1, 10-14, 23-32			
	Indu	ustrial ap	oplicability (IA)	Yes:	Claims	1, 10-14, 23-32			
			. •	No:	Claims				
2.	Cita	itions an	d explanations						

see separate sheet

#### Re Item IV

#### Lack of unity of invention

The separate inventions/groups of invention are:

Invention 1: Claims 1 and 14 completely and claims 10 to 13, 23 to 32 partially.

Nucleic acid sequence encoding a 75kD Lawsonia intracellularis protein or a part of said nucleic acid sequence that encodes an immunogenic fragment of said protein said nucleic acid sequence, or said part thereof having at least 90% homology with the nucleic acid sequence as depicted in SEQ ID NO: 1, protein that is at least 90% homologous to SEQ ID NO: 2, live recombinant carrier, host cell, vaccine comprising said nucleic acid, use of said protein in the manufacture of a vaccine and method of preparing said vaccine, diagnostic tests involving said nucleic acid or proteins.

Invention 2: Claims 2 and 15 completely and claims 10 to 13, 23 to 32 partially.

Nucleic acid sequence encoding a 27kD Lawsonia intracellularis protein or a part of said nucleic acid sequence that encodes an immunogenic fragment of said protein said nucleic acid sequence, or said part thereof having at least 90% homology with the nucleic acid sequence as depicted in SEQ ID NO: 3, protein that is at least 90% homologous to SEQ ID NO: 4, live recombinant carrier, host cell, vaccine comprising said nucleic acid, use of said protein in the manufacture of a vaccine and method of preparing said vaccine, diagnostic tests involving said nucleic acid or proteins.

Invention 3: Claims 3 and 16 completely and claims 10 to 13, 23 to 32 partially. Nucleic acid sequence encoding a 62kD Lawsonia intracellularis protein or a part of said nucleic acid sequence that encodes an immunogenic fragment of said protein said nucleic acid sequence, or said part thereof having at least 90% homology with the nucleic acid sequence as depicted in SEQ ID NO: 5, protein that is at least 90% homologous to SEQ ID NO: 6, live recombinant carrier, host cell, vaccine comprising said nucleic acid, use of said protein in the manufacture of a vaccine and method of preparing said vaccine, diagnostic tests involving said nucleic acid or proteins.

Invention 4: Claims 4 and 17 completely and claims 10 to 13, 23 to 32 partially.

Nucleic acid sequence encoding a 57kD Lawsonia intracellularis protein or a part of said nucleic acid sequence that encodes an immunogenic fragment of said protein said nucleic

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acid sequence, or said part thereof having at least 90% homology with the nucleic acid sequence as depicted in SEQ ID NO: 7, protein that is at least 90% homologous to SEQ ID NO: 8, live recombinant carrier, host cell, vaccine comprising said nucleic acid, use of said protein in the manufacture of a vaccine and method of preparing said vaccine, diagnostic tests involving said nucleic acid or proteins.

Invention 5: Claims 5 and 18 completely and claims 10 to 13, 23 to 32 partially. Nucleic acid sequence encoding a 74kD Lawsonia intracellularis protein or a part of said nucleic acid sequence that encodes an immunogenic fragment of said protein said nucleic acid sequence, or said part thereof having at least 90% homology with the nucleic acid sequence as depicted in SEQ ID NO: 9, protein that is at least 90% homologous to SEQ ID NO: 10, live recombinant carrier, host cell, vaccine comprising said nucleic acid, use of said protein in the manufacture of a vaccine and method of preparing said vaccine, diagnostic tests involving said nucleic acid or proteins.

Invention 6: Claims 6 and 19 completely and claims 10 to 13, 23 to 32 partially. Nucleic acid sequence encoding a 44kD Lawsonia intracellularis protein or a part of said nucleic acid sequence that encodes an immunogenic fragment of said protein said nucleic acid sequence, or said part thereof having at least 90% homology with the nucleic acid sequence as depicted in SEQ ID NO: 11, protein that is at least 90% homologous to SEQ ID NO: 12, live recombinant carrier, host cell, vaccine comprising said nucleic acid, use of said protein in the manufacture of a vaccine and method of preparing said vaccine, diagnostic tests involving said nucleic acid or proteins.

Invention 7: Claims 7 and 20 completely and claims 10 to 13, 23 to 32 partially. Nucleic acid sequence encoding a 43kD *Lawsonia intracellularis* protein or a part of said nucleic acid sequence that encodes an immunogenic fragment of said protein said nucleic acid sequence, or said part thereof having at least 90% homology with the nucleic acid sequence as depicted in SEQ ID NO: 13, protein that is at least 90% homologous to SEQ ID NO: 14, live recombinant carrier, host cell, vaccine comprising said nucleic acid, use of said protein in the manufacture of a vaccine and method of preparing said vaccine, diagnostic tests involving said nucleic acid or proteins.

Invention 8: Claims 8 and 21 completely and claims 10 to 13, 23 to 32 partially.

Nucleic acid sequence encoding a 26/31kD Lawsonia intracellularis protein or a part of said nucleic acid sequence that encodes an immunogenic fragment of said protein said nucleic acid sequence, or said part thereof having at least 90% homology with the nucleic acid sequence as depicted in SEQ ID NO: 15, protein that is at least 90% homologous to SEQ ID NO: 16, live recombinant carrier, host cell, vaccine comprising said nucleic acid, use of said protein in the manufacture of a vaccine and method of preparing said vaccine, diagnostic tests involving said nucleic acid or proteins.

Invention 9: Claims 9 and 22 completely and claims 10 to 13, 23 to 32 partially. Nucleic acid sequence encoding a 101kD Lawsonia intracellularis protein or a part of said nucleic acid sequence that encodes an immunogenic fragment of said protein said nucleic acid sequence, or said part thereof having at least 90% homology with the nucleic acid sequence as depicted in SEQ ID NO: 17, protein that is at least 90% homologous to SEQ ID NO: 18, live recombinant carrier, host cell, vaccine comprising said nucleic acid, use of said protein in the manufacture of a vaccine and method of preparing said vaccine, diagnostic tests involving said nucleic acid or proteins.

The general concept of characterizing nucleic acids which encode *Lawsonia intracellularis* proteins as using them in vaccines against *Lawsonia intracellularis* is already known from the prior art document D1: EP-A-1 219 711 (Akzo Nobel N.V.) and D2: WO-A-0 226 250 (Arizona Board of Regents on behalf of the University of Arizona.)

D1 discloses nucleic acid sequences encoding *Lawsonia intracellularis* outer membrane proteins and immunogenic fragments for use as vaccines against *Lawsonia intracellularis*. D2 describes vaccines against proliferative ileitis containing protective immunogenic subunits of *Lawsonia intracellularis*.

Due to the fact that the common unifying concept is known in the state of the art, there appears therefore to be no technical features in common between the different inventions involving different nucleotide and amino acid sequences, that could provide a novel and inventive unifying concept.

Consequently, the requisite unity of invention (Rule 13.1 PCT) therefore

no longer exists inasmuch as a technical relationship involving one or more of the same or corresponding special technical features in the sense of Rule 13.2 PCT does not exist between the subject-matter of the groups of claims.

#### Re Item V

Reasoned statement with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

#### Examination of:

Invention 1: Claims 1 and 14 completely and claims 10 to 13, 23 to 32 partially.

Nucleic acid sequence encoding a 75kD Lawsonia intracellularis protein or a part of said nucleic acid sequence that encodes an immunogenic fragment of said protein said nucleic acid sequence, or said part thereof having at least 90% homology with the nucleic acid sequence as depicted in SEQ ID NO: 1, protein that is at least 90% homologous to SEQ ID NO: 2, live recombinant carrier, host cell, vaccine comprising said nucleic acid, use of said protein in the manufacture of a vaccine and method of preparing said vaccine, diagnostic tests involving said nucleic acid or proteins.

- The following **documents** are referred to in this communication; the numbering will be adhered to in the rest of the procedure:
  - D1: EP-A-1 219 711 (Akzo Nobel N.V.)
- D2: WO-A-0 226 250 (Arizona Board of Regents on behalf of the University of Arizona.)
- 2 **NOVELTY** (Art. 33(2) PCT)
- 2.1 In view of the prior art cited, claims 1 and 14 and claims dependent thereon appear to be novel and meet therefore the requirements of Art.33(2) PCT, since

the nucleic and amino acid sequences SEQ ID NOs: 1 and 2 are not disclosed in the state of the art.

### 3 **INVENTIVE STEP** (Art. 33(3) PCT)

- 3.1 Documents D2 and D3 are considered to represent the most relevant state of the art. D2 discloses nucleic acid sequences encoding *Lawsonia intracellularis* outer membrane proteins and immunogenic fragments for use as vaccines against *Lawsonia intracellularis*. D3 describes vaccines against proliferative ileitis containing protective immunogenic subunits of *Lawsonia intracellularis*.
- 3.2 The subject-matter of the present application and claims 1 and 14 and claims dependent thereon involve different nucleic acid sequences and their use as immunogenic fragments as vaccines against *Lawsonia intracellularis*.
- 3.3 The problem may be defined as the provision of alternative nucleic acid sequences and immunogenic fragments for use as vaccines against *Lawsonia intracellularis*.
- 3.4 However due to the fact that the above problem has previously been solved by the subunit vaccines of the state of the art and that there is no evidence in the description that the nucleic or amino acid sequences SEQ ID NOs: 1 and 2 actually solve the problem through initiating an effective protective immune response to *Lawsonia intracellularis*, the subject-matter of claims 1 and 14 cannot be recognized as involving an inventive step according to Article 33(3) PCT.
- Dependent claims 10 to 13, 23 to 32, as far as they are dependent upon claims 1 and 14, do not appear to contain any additional features which, in combination with the features of any claim to which they refer, involve an inventive step.
- In view of the above, the present application does not meet the requirements of Article 33(3) PCT, because the subject-matter of claims 1, 10 to 14, 23 to 32 does

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not involve an inventive step.

For the assessment of the present claims 23 and 24 on the question whether they are industrially applicable, no unified criteria exist in the PCT Contracting States. The patentability can also be dependent upon the formulation of the claims. The EPO, for example, does not recognize as industrially applicable the subject-matter of claims to the use of a compound in medical treatment, but may allow, however, claims to a known compound for first use in medical treatment and the use of such a compound for the manufacture of a medicament for a new medical treatment.

### **PATENT COOPERATION TREATY**

From INTER	the RNATIONAL SEAF	RCHING AUTH	ORITY		WIPO PCT			
To:				PCT				
	see form F	PCT/ISA/220		WRITTEN OPINION OF THE INTERNATIONAL SEARCHING AUTHORITY (PCT Rule 43 <i>bis</i> .1)				
				Date of mailing (day/month/year) see	o form PCT/ISA/210 (second sheet)			
• •	cant's or agent's file form PCT/ISA/22			FOR FURTHER A See paragraph 2 below				
	ational application N /EP2005/000562		International filing date (da 18.01.2005	ay/month/year)	Priority date (day/month/year) 22.01.2004			
Intern C07	International Patent Classification (IPC) or both national classification and IPC C07K14/195, C12N15/31, C07K16/12, C12Q1/68, A61K39/02							
Appli AKZ	cant O NOBEL N.V.							
1.	This opinion co	ntains indicati	ons relating to the follo	wing items:				
	⊠ Box No. I	Basis of the op	alalon					
	Box No. II	Priority	,,,,,,o,,,		,			
	Box No. III		ment of opinion with regal	rd to novelty, inventiv	e step and industrial applicability			
	☑ Box No. IV	Lack of unity o						
	☑ Box No. V	Resconed stat	ement under Rule 43 <i>bis</i> .	bis.1(a)(l) with regard to novelty, inventive step or industrial ons supporting such statement				
	☐ Box Nö. VI	Certain docum	ents cited		•			
	☐ Box No. VII		s in the international appl					
	☐ Box No. VIII	Certain observ	ations on the internations	al application				
2.	FURTHER ACTI	•						
	If a demand for international preliminary examination is made, this opinion will usually be considered to be a written opinion of the International Preliminary Examining Authority ("IPEA"). However, this does not apply where the applicant chooses an Authority other than this one to be the IPEA and the chosen IPEA has notifed the International Bureau under Rule 66.1 bis(b) that written opinions of this International Searching Authority will not be so considered.							
	If this opinion is, as provided above, considered to be a written opinion of the IPEA, the applicant is invited to submit to the IPEA a written reply together, where appropriate, with amendments, before the expiration of three months from the date of mailing of Form PCT/ISA/220 or before the expiration of 22 months from the priority date, whichever expires later.							
	For further option	ns, see Form Po		. •				
3.	For further detail	ls, see notes to	Form PCT/ISA/220.					
Nam	e and mailing addre	ss of the ISA:		Authorized Officer	and the state of t			

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European Patent Office - P.B. 5818 Patentlaan 2 NL-2280 HV Rijswijk - Pays Bas Tel. +31 70 340 - 2040 Tx: 31 651 epo nl Fax: +31 70 340 - 3016 Hix, R

Telephone No. +31 70 340-3898



International application No. PCT/EP2005/000562

_	Box	c N	o. I Basis of the opinion							
1.	With regard to the language, this opinion has been established on the basis of the international application in the language in which it was filed, unless otherwise indicated under this item.									
	This opinion has been established on the basis of a translation from the original language into the following language , which is the language of a translation furnished for the purposes of international search (under Rules 12.3 and 23.1(b)).									
2.	. With regard to any <b>nucleotide</b> and/or amino acid sequence disclosed in the international application and necessary to the claimed invention, this opinion has been established on the basis of:									
	a. ty	pe	of material:							
	٥	₃	a sequence listing							
		<b>_</b>	table(s) related to the sequence listing							
	b. fc	m	at of material:							
	Ĺ	3	in written format							
	D	3	in computer readable form							
	c. tir	ne	of filing/furnishing:							
	D	₫	contained in the international application as filed.							
	Σ	3	filed together with the international application in computer readable form.							
	C	3	furnished subsequently to this Authority for the purposes of search.							
3.		ha	addition, in the case that more than one version or copy of a sequence listing and/or table relating thereto is been filed or furnished, the required statements that the information in the subsequent or additional bies is identical to that in the application as filed or does not go beyond the application as filed, as propriate, were furnished.							
4.	Add	itio	nal comments:							

International application No. PCT/EP2005/000562

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	Bo	x No. IV	Lack of unity of	inventio	n					
1.		☐ In response to the invitation (Form PCT/ISA/206) to pay additional fees, the applicant has:								
			paid additional fee	s.			,			
			paid additional fee	s under pr	rotest.					
			not paid additional	fees.						
2.			uthority found that to olicant to pay addition		ment of un	ity of invention is no	t complied with and	chose not to invite		
3.	This	This Authority considers that the requirement of unity of invention in accordance with Rule 13.1, 13.2 and 13.3 is								
	☐ complied with									
	☑ not complied with for the following reasons:									
	see separate sheet									
4.	Consequently, this report has been established in respect of the following parts of the international application:									
	□ all parts.									
	<b>1</b>	the parts	s relating to claims l	Nos. 1, 10	-14, 23-32	,				
					٠					
	Box	No. V ustrial a	Reasoned state applicability; citati	ment und ons and e	er Rule 43 explanatio	B <i>bis</i> .1(a)(i) with regains supporting sucl	ard to novelty, invention in the statement	entive step or		
1.	Sta	tement			•					
	Nov	elty (N)		Yes: No:	Claims Claims	1, 10-14, 23-32				
	Inve	entive st	ep (IS)	Yes: No:	Claims Claims	1, 10-14, 23-32	-			
	Indi	ustrial a	pplicability (IA)	Yes: No:	Claims Claims	1, 10-14, 23-32				
2.	Cita	ntions ar	nd explanations							

see separate sheet.

#### Re Item IV

### Lack of unity of invention

The separate inventions/groups of invention are:

Invention 1: Claims 1 and 14 completely and claims 10 to 13, 23 to 32 partially.

Nucleic acid sequence encoding a 75kD *Lawsonia intracellularis* protein or a part of said nucleic acid sequence that encodes an immunogenic fragment of said protein said nucleic acid sequence, or said part thereof having at least 90% homology with the nucleic acid sequence as depicted in SEQ ID NO: 1, protein that is at least 90% homologous to SEQ ID NO: 2, live recombinant carrier, host cell, vaccine comprising said nucleic acid, use of said protein in the manufacture of a vaccine and method of preparing said vaccine, diagnostic tests involving said nucleic acid or proteins.

Invention 2: Claims 2 and 15 completely and claims 10 to 13, 23 to 32 partially.

Nucleic acid sequence encoding a 27kD Lawsonia intracellularis protein or a part of said nucleic acid sequence that encodes an immunogenic fragment of said protein said nucleic acid sequence, or said part thereof having at least 90% homology with the nucleic acid sequence as depicted in SEQ ID NO: 3, protein that is at least 90% homologous to SEQ ID NO: 4, live recombinant carrier, host cell, vaccine comprising said nucleic acid, use of said protein in the manufacture of a vaccine and method of preparing said vaccine, diagnostic tests involving said nucleic acid or proteins.

Invention 3: Claims 3 and 16 completely and claims 10 to 13, 23 to 32 partially. Nucleic acid sequence encoding a 62kD *Lawsonia intracellularis* protein or a part of said nucleic acid sequence that encodes an immunogenic fragment of said protein said nucleic acid sequence, or said part thereof having at least 90% homology with the nucleic acid sequence as depicted in SEQ ID NO: 5, protein that is at least 90% homologous to SEQ ID NO: 6, live recombinant carrier, host cell, vaccine comprising said nucleic acid, use of said protein in the manufacture of a vaccine and method of preparing said vaccine, diagnostic tests involving said nucleic acid or proteins.

Invention 4: Claims 4 and 17 completely and claims 10 to 13, 23 to 32 partially.

Nucleic acid sequence encoding a 57kD Lawsonia intracellularis protein or a part of said nucleic acid sequence that encodes an immunogenic fragment of said protein said nucleic

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acid sequence, or said part thereof having at least 90% homology with the nucleic acid sequence as depicted in SEQ ID NO: 7, protein that is at least 90% homologous to SEQ ID NO: 8, live recombinant carrier, host cell, vaccine comprising said nucleic acid, use of said protein in the manufacture of a vaccine and method of preparing said vaccine, diagnostic tests involving said nucleic acid or proteins.

Invention 5: Claims 5 and 18 completely and claims 10 to 13, 23 to 32 partially.

Nucleic acid sequence encoding a 74kD Lawsonia intracellularis protein or a part of said nucleic acid sequence that encodes an immunogenic fragment of said protein said nucleic acid sequence, or said part thereof having at least 90% homology with the nucleic acid sequence as depicted in SEQ ID NO: 9, protein that is at least 90% homologous to SEQ ID NO: 10, live recombinant carrier, host cell, vaccine comprising said nucleic acid, use of said protein in the manufacture of a vaccine and method of preparing said vaccine, diagnostic tests involving said nucleic acid or proteins.

Invention 6: Claims 6 and 19 completely and claims 10 to 13, 23 to 32 partially. Nucleic acid sequence encoding a 44kD Lawsonia intracellularis protein or a part of said nucleic acid sequence that encodes an immunogenic fragment of said protein said nucleic acid sequence, or said part thereof having at least 90% homology with the nucleic acid sequence as depicted in SEQ ID NO: 11, protein that is at least 90% homologous to SEQ ID NO: 12, live recombinant carrier, host cell, vaccine comprising said nucleic acid, use of said protein in the manufacture of a vaccine and method of preparing said vaccine, diagnostic tests involving said nucleic acid or proteins.

Invention 7: Claims 7 and 20 completely and claims 10 to 13, 23 to 32 partially. Nucleic acid sequence encoding a 43kD Lawsonia intracellularis protein or a part of said nucleic acid sequence that encodes an immunogenic fragment of said protein said nucleic acid sequence, or said part thereof having at least 90% homology with the nucleic acid sequence as depicted in SEQ ID NO: 13, protein that is at least 90% homologous to SEQ ID NO: 14, live recombinant carrier, host cell, vaccine comprising said nucleic acid, use of said protein in the manufacture of a vaccine and method of preparing said vaccine, diagnostic tests involving said nucleic acid or proteins.

Invention 8: Claims 8 and 21 completely and claims 10 to 13, 23 to 32 partially.

Nucleic acid sequence encoding a 26/31kD Lawsonia intracellularis protein or a part of said nucleic acid sequence that encodes an immunogenic fragment of said protein said nucleic acid sequence, or said part thereof having at least 90% homology with the nucleic acid sequence as depicted in SEQ ID NO: 15, protein that is at least 90% homologous to SEQ ID NO: 16, live recombinant carrier, host cell, vaccine comprising said nucleic acid, use of said protein in the manufacture of a vaccine and method of preparing said vaccine, diagnostic tests involving said nucleic acid or proteins.

Invention 9: Claims 9 and 22 completely and claims 10 to 13, 23 to 32 partially. Nucleic acid sequence encoding a 101kD Lawsonia intracellularis protein or a part of said nucleic acid sequence that encodes an immunogenic fragment of said protein said nucleic acid sequence, or said part thereof having at least 90% homology with the nucleic acid sequence as depicted in SEQ ID NO: 17, protein that is at least 90% homologous to SEQ ID NO: 18, live recombinant carrier, host cell, vaccine comprising said nucleic acid, use of said protein in the manufacture of a vaccine and method of preparing said vaccine, diagnostic tests involving said nucleic acid or proteins.

The general concept of characterizing nucleic acids which encode *Lawsonia intracellularis* proteins as using them in vaccines against *Lawsonia intracellularis* is already known from the prior art document D1: EP-A-1 219 711 (Akzo Nobel N.V.) and D2: WO-A-0 226 250 (Arizona Board of Regents on behalf of the University of Arizona.)

D1 discloses nucleic acid sequences encoding *Lawsonia intracellularis* outer membrane proteins and immunogenic fragments for use as vaccines against *Lawsonia intracellularis*. D2 describes vaccines against proliferative ileitis containing protective immunogenic subunits of *Lawsonia intracellularis*.

Due to the fact that the common unifying concept is known in the state of the art, there appears therefore to be no technical features in common between the different inventions involving different nucleotide and amino acid sequences, that could provide a novel and inventive unifying concept.

Consequently, the requisite unity of invention (Rule 13.1 PCT) therefore

no longer exists inasmuch as a technical relationship involving one or more of the same or corresponding special technical features in the sense of Rule 13.2 PCT does not exist between the subject-matter of the groups of claims.

#### Re Item V

Reasoned statement with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

#### Examination of:

Invention 1: Claims 1 and 14 completely and claims 10 to 13, 23 to 32 partially.

Nucleic acid sequence encoding a 75kD Lawsonia intracellularis protein or a part of said nucleic acid sequence that encodes an immunogenic fragment of said protein said nucleic acid sequence, or said part thereof having at least 90% homology with the nucleic acid sequence as depicted in SEQ ID NO: 1, protein that is at least 90% homologous to SEQ ID NO: 2, live recombinant carrier, host cell, vaccine comprising said nucleic acid, use of said protein in the manufacture of a vaccine and method of preparing said vaccine, diagnostic tests involving said nucleic acid or proteins.

- The following **documents** are referred to in this communication; the numbering will be adhered to in the rest of the procedure:
  - D1: EP-A-1 219 711 (Akzo Nobel N.V.)
- D2: WO-A-0 226 250 (Arizona Board of Regents on behalf of the University of Arizona.)
- 2 NOVELTY (Art. 33(2) PCT)
- 2.1 In view of the prior art cited, claims 1 and 14 and claims dependent thereon appear to be novel and meet therefore the requirements of Art.33(2) PCT, since

the nucleic and amino acid sequences SEQ ID NOs: 1 and 2 are not disclosed in the state of the art.

#### 3 INVENTIVE STEP (Art. 33(3) PCT)

- 3.1 Documents D2 and D3 are considered to represent the most relevant state of the art. D2 discloses nucleic acid sequences encoding *Lawsonia intracellularis* outer membrane proteins and immunogenic fragments for use as vaccines against *Lawsonia intracellularis*. D3 describes vaccines against proliferative ileitis containing protective immunogenic subunits of *Lawsonia intracellularis*.
- 3.2 The subject-matter of the present application and claims 1 and 14 and claims dependent thereon involve different nucleic acid sequences and their use as immunogenic fragments as vaccines against *Lawsonia intracellularis*.
- 3.3 The problem may be defined as the provision of alternative nucleic acid sequences and immunogenic fragments for use as vaccines against *Lawsonia intracellularis*.
- 3.4 However due to the fact that the above problem has previously been solved by the subunit vaccines of the state of the art and that there is no evidence in the description that the nucleic or amino acid sequences SEQ ID NOs: 1 and 2 actually solve the problem through initiating an effective protective immune response to *Lawsonia intracellularis*, the subject-matter of claims 1 and 14 cannot be recognized as involving an inventive step according to Article 33(3) PCT.
- Dependent claims 10 to 13, 23 to 32, as far as they are dependent upon claims 1 and 14, do not appear to contain any additional features which, in combination with the features of any claim to which they refer, involve an inventive step.
- 3.6 In view of the above, the present application does not meet the requirements of Article 33(3) PCT, because the subject-matter of claims 1, 10 to 14, 23 to 32 does

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not involve an inventive step.

For the assessment of the present claims 23 and 24 on the question whether they are industrially applicable, no unified criteria exist in the PCT Contracting States. The patentability can also be dependent upon the formulation of the claims. The EPO, for example, does not recognize as industrially applicable the subject-matter of claims to the use of a compound in medical treatment, but may allow, however, claims to a known compound for first use in medical treatment and the use of such a compound for the manufacture of a medicament for a new medical treatment.

### **PATENT COOPERATION TREATY**

From	the RNATIONAL SEA	RCHING AUTH	ORITY	WIPO PCT			
То:					PCT		
	see form	PCT/ISA/220		WRITTEN OPINION OF THE INTERNATIONAL SEARCHING AUTHORITY (PCT Rule 43bis.1)			
<u></u>				Date of mailing (day/month/year)	see form PCT/ISA/210 (second sheet)		
	cant's or agent's file form PCT/ISA/2			FOR FURTHER See paragraph 2 b			
PCT	national application I/EP2005/00056	2 ·	International filing date (c 18.01.2005		Priority date (day/month/year) 22.01.2004		
			both national classification /12, C12Q1/68, A61K				
Appli AKZ	cant O NOBEL N.V.						
1	This opinion co	ontains indication	ons relating to the follo	owing items:			
	☑ Box No. 1	Basis of the op	inion				
ĺ	☐ Box No. II	Priority					
	☐ Box No. III	Non-establishn	nent of opinion with rega	ard to novelty, inven	tive step and industrial applicability		
	Box No. IV	Lack of unity o	f invention				
	☑ Box No. V	Reasoned stat applicability; ci	ement under Rule 43 <i>bis</i> tations and explanations	:.1(a)(l) with regard s supporting such st	to novelty, inventive step or industrial atement		
	☐ Box No. VI	Certain docum					
	☐ Box No. VII		in the international app	,			
	☐ Box No. VIII	Certain observ	ations on the internation	al application			
2.	FURTHER ACT	ION	,		•		
	If a demand for international preliminary examination is made, this opinion will usually be considered to be a written opinion of the International Preliminary Examining Authority ("IPEA"). However, this does not apply where the applicant chooses an Authority other than this one to be the IPEA and the chosen IPEA has notified the International Bureau under Rule 66.1 bis(b) that written opinions of this International Searching Authority will not be so considered.						
If this opinion is, as provided above, considered to be a written opinion submit to the IPEA a written reply together, where appropriate, with months from the date of mailing of Form PCT/ISA/220 or before the whichever expires later.					nents, before the expiration of three		
	For further option	ns, see Form PC	T/ISA/220.		·		
3.	For further detail	ls, see notes to l	Form PCT/ISA/220.				
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Name and mailing address of the ISA:



European Patent Office - P.B. 5818 Patentlaan 2 NL-2280 HV Rijswijk - Pays Bas Tel. +31 70 340 - 2040 Tx: 31 651 epo nl Fax: +31 70 340 - 3016 Authorized Officer

Hix, R

Telephone No. +31 70 340-3898



International application No. PCT/EP2005/000562

_	Box	x N	<u>o. I</u>	Basis of the opinion
1.	Witl the	h re lan	garo gua(	d to the language, this opinion has been established on the basis of the international application in ge in which it was filed, unless otherwise indicated under this item.
		lar	ngua	pinion has been established on the basis of a translation from the original language into the following to ge , which is the language of a translation furnished for the purposes of international search Rules 12.3 and 23.1(b)).
2.				d to any <b>nucleotide and/or amino acid sequence</b> disclosed in the international application and to the claimed invention, this opinion has been established on the basis of:
	a. ty	/ре	of m	naterial:
	6	⊠	a se	equence listing
	. [	3	tabl	e(s) related to the sequence listing
	b. fc	m	at of	f material:
	D	₫	in w	vritten format
	D	3	in c	omputer readable form
	c. tir	me	of fil	ling/furnishing:
	Σ	⊴	con	tained in the international application as filed.
	Σ	3	filec	together with the international application in computer readable form.
		3	fum	ished subsequently to this Authority for the purposes of search.
3.		has	s bed oies	tion, in the case that more than one version or copy of a sequence listing and/or table relating thereto en filed or furnished, the required statements that the information in the subsequent or additional is identical to that in the application as filed or does not go beyond the application as filed, as riate, were furnished.
1	Δdd	itior	nal c	comments:

International application No. PCT/EP2005/000562

	Во	x No. IV	Lack of unity of	inventio	n						
1.		In resp	onse to the invitation	n (Form F	PCT/ISA/20	6) to pay additional t	fees, the a	applicant ha	ıs:		
		Ċ	paid additional fee	s.	•						
			paid additional fee	s under pi	otest.		٠,				
			not paid additional	fees.							
2.			uthority found that to olicant to pay addition		ment of un	ity of invention is no	t complied	f with and c	hose not to	invite	
3.	This Authority considers that the requirement of unity of invention in accordance with Rule 13.1, 13.2 and 13.3 is										
	☐ complied with										
	×	not com	plied with for the fo	lied with for the following reasons:							
		see se	parate sheet				•	-	•		
4.	Cor	Consequently, this report has been established in respect of the following parts of the international application:									
		all parts			•						
		the parts	s relating to claims								
					•						
	Bo	x No. V ustrial a	Reasoned state applicability; citati	ment und ons and e	er Rule 43 explanation	<i>bis.</i> 1(a)(i) with reg	ard to no	velty, inver	ntive step o	r	
1.	Sta	tement	,		٠			. •			
	Nov	velty (N)		Yes: No:	Claims Claims	1, 10-14, 23-32	•				
	Inve	entive st	ep (IS)	Yes: No:	Claims Claims	1, 10-14, 23-32					
	Indi	ustrial a	pplicability (IA)	Yes: No:	Claims Claims	1, 10-14, 23-32				. •	
										•	

2. Citations and explanations

see separate sheet

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#### Re Item IV

### Lack of unity of invention

The separate inventions/groups of invention are:

Invention 1: Claims 1 and 14 completely and claims 10 to 13, 23 to 32 partially.

Nucleic acid sequence encoding a 75kD *Lawsonia intracellularis* protein or a part of said nucleic acid sequence that encodes an immunogenic fragment of said protein said nucleic acid sequence, or said part thereof having at least 90% homology with the nucleic acid sequence as depicted in SEQ ID NO: 1, protein that is at least 90% homologous to SEQ ID NO: 2, live recombinant carrier, host cell, vaccine comprising said nucleic acid, use of said protein in the manufacture of a vaccine and method of preparing said vaccine, diagnostic tests involving said nucleic acid or proteins.

Invention 2: Claims 2 and 15 completely and claims 10 to 13, 23 to 32 partially.

Nucleic acid sequence encoding a 27kD Lawsonia intracellularis protein or a part of said nucleic acid sequence that encodes an immunogenic fragment of said protein said nucleic acid sequence, or said part thereof having at least 90% homology with the nucleic acid sequence as depicted in SEQ ID NO: 3, protein that is at least 90% homologous to SEQ ID NO: 4, live recombinant carrier, host cell, vaccine comprising said nucleic acid, use of said protein in the manufacture of a vaccine and method of preparing said vaccine, diagnostic tests involving said nucleic acid or proteins.

Invention 3: Claims 3 and 16 completely and claims 10 to 13, 23 to 32 partially. Nucleic acid sequence encoding a 62kD Lawsonia intracellularis protein or a part of said nucleic acid sequence that encodes an immunogenic fragment of said protein said nucleic acid sequence, or said part thereof having at least 90% homology with the nucleic acid sequence as depicted in SEQ ID NO: 5, protein that is at least 90% homologous to SEQ ID NO: 6, live recombinant carrier, host cell, vaccine comprising said nucleic acid, use of said protein in the manufacture of a vaccine and method of preparing said vaccine, diagnostic tests involving said nucleic acid or proteins.

Invention 4: Claims 4 and 17 completely and claims 10 to 13, 23 to 32 partially.

Nucleic acid sequence encoding a 57kD Lawsonia intracellularis protein or a part of said nucleic acid sequence that encodes an immunogenic fragment of said protein said nucleic

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acid sequence, or said part thereof having at least 90% homology with the nucleic acid sequence as depicted in SEQ ID NO: 7, protein that is at least 90% homologous to SEQ ID NO: 8, live recombinant carrier, host cell, vaccine comprising said nucleic acid, use of said protein in the manufacture of a vaccine and method of preparing said vaccine, diagnostic tests involving said nucleic acid or proteins.

Invention 5: Claims 5 and 18 completely and claims 10 to 13, 23 to 32 partially.

Nucleic acid sequence encoding a 74kD Lawsonia intracellularis protein or a part of said nucleic acid sequence that encodes an immunogenic fragment of said protein said nucleic acid sequence, or said part thereof having at least 90% homology with the nucleic acid sequence as depicted in SEQ ID NO: 9, protein that is at least 90% homologous to SEQ ID NO: 10, live recombinant carrier, host cell, vaccine comprising said nucleic acid, use of said protein in the manufacture of a vaccine and method of preparing said vaccine, diagnostic tests involving said nucleic acid or proteins.

Invention 6: Claims 6 and 19 completely and claims 10 to 13, 23 to 32 partially. Nucleic acid sequence encoding a 44kD Lawsonia intracellularis protein or a part of said nucleic acid sequence that encodes an immunogenic fragment of said protein said nucleic acid sequence, or said part thereof having at least 90% homology with the nucleic acid sequence as depicted in SEQ ID NO: 11, protein that is at least 90% homologous to SEQ ID NO: 12, live recombinant carrier, host cell, vaccine comprising said nucleic acid, use of said protein in the manufacture of a vaccine and method of preparing said vaccine, diagnostic tests involving said nucleic acid or proteins.

Invention 7: Claims 7 and 20 completely and claims 10 to 13, 23 to 32 partially. Nucleic acid sequence encoding a 43kD Lawsonia intracellularis protein or a part of said nucleic acid sequence that encodes an immunogenic fragment of said protein said nucleic acid sequence, or said part thereof having at least 90% homology with the nucleic acid sequence as depicted in SEQ ID NO: 13, protein that is at least 90% homologous to SEQ ID NO: 14, live recombinant carrier, host cell, vaccine comprising said nucleic acid, use of said protein in the manufacture of a vaccine and method of preparing said vaccine, diagnostic tests involving said nucleic acid or proteins.

Invention 8: Claims 8 and 21 completely and claims 10 to 13, 23 to 32 partially.

Nucleic acid sequence encoding a 26/31kD *Lawsonia intracellularis* protein or a part of said nucleic acid sequence that encodes an immunogenic fragment of said protein said nucleic acid sequence, or said part thereof having at least 90% homology with the nucleic acid sequence as depicted in SEQ ID NO: 15, protein that is at least 90% homologous to SEQ ID NO: 16, live recombinant carrier, host cell, vaccine comprising said nucleic acid, use of said protein in the manufacture of a vaccine and method of preparing said vaccine, diagnostic tests involving said nucleic acid or proteins.

Invention 9: Claims 9 and 22 completely and claims 10 to 13, 23 to 32 partially. Nucleic acid sequence encoding a 101kD Lawsonia intracellularis protein or a part of said nucleic acid sequence that encodes an immunogenic fragment of said protein said nucleic acid sequence, or said part thereof having at least 90% homology with the nucleic acid sequence as depicted in SEQ ID NO: 17, protein that is at least 90% homologous to SEQ ID NO: 18, live recombinant carrier, host cell, vaccine comprising said nucleic acid, use of said protein in the manufacture of a vaccine and method of preparing said vaccine, diagnostic tests involving said nucleic acid or proteins.

The general concept of characterizing nucleic acids which encode *Lawsonia intracellularis* proteins as using them in vaccines against *Lawsonia intracellularis* is already known from the prior art document D1: EP-A-1 219 711 (Akzo Nobel N.V.) and D2: WO-A-0 226 250 (Arizona Board of Regents on behalf of the University of Arizona.)

D1 discloses nucleic acid sequences encoding *Lawsonia intracellularis* outer membrane proteins and immunogenic fragments for use as vaccines against *Lawsonia intracellularis*. D2 describes vaccines against proliferative ileitis containing protective immunogenic subunits of *Lawsonia intracellularis*.

Due to the fact that the common unifying concept is known in the state of the art, there appears therefore to be no technical features in common between the different inventions involving different nucleotide and amino acid sequences, that could provide a novel and inventive unifying concept.

Consequently, the requisite unity of invention (Rule 13.1 PCT) therefore

no longer exists inasmuch as a technical relationship involving one or more of the same or corresponding special technical features in the sense of Rule 13.2 PCT does not exist between the subject-matter of the groups of claims.

#### Re Item V

Reasoned statement with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

#### Examination of:

Invention 1: Claims 1 and 14 completely and claims 10 to 13, 23 to 32 partially.

Nucleic acid sequence encoding a 75kD Lawsonia intracellularis protein or a part of said nucleic acid sequence that encodes an immunogenic fragment of said protein said nucleic acid sequence, or said part thereof having at least 90% homology with the nucleic acid sequence as depicted in SEQ ID NO: 1, protein that is at least 90% homologous to SEQ ID NO: 2, live recombinant carrier, host cell, vaccine comprising said nucleic acid, use of said protein in the manufacture of a vaccine and method of preparing said vaccine, diagnostic tests involving said nucleic acid or proteins.

- The following **documents** are referred to in this communication; the numbering will be adhered to in the rest of the procedure:
  - D1: EP-A-1 219 711 (Akzo Nobel N.V.)
- D2: WO-A-0 226 250 (Arizona Board of Regents on behalf of the University of Arizona.)
- 2 **NOVELTY** (Art. 33(2) PCT)
- 2.1 In view of the prior art cited, claims 1 and 14 and claims dependent thereon appear to be novel and meet therefore the requirements of Art.33(2) PCT, since

the nucleic and amino acid sequences SEQ ID NOs: 1 and 2 are not disclosed in the state of the art.

#### 3 INVENTIVE STEP (Art. 33(3) PCT)

- 3.1 Documents D2 and D3 are considered to represent the most relevant state of the art. D2 discloses nucleic acid sequences encoding *Lawsonia intracellularis* outer membrane proteins and immunogenic fragments for use as vaccines against *Lawsonia intracellularis*. D3 describes vaccines against proliferative ileitis containing protective immunogenic subunits of *Lawsonia intracellularis*.
- 3.2 The subject-matter of the present application and claims 1 and 14 and claims dependent thereon involve different nucleic acid sequences and their use as immunogenic fragments as vaccines against *Lawsonia intracellularis*.
- 3.3 The problem may be defined as the provision of alternative nucleic acid sequences and immunogenic fragments for use as vaccines against *Lawsonia intracellularis*.
- 3.4 However due to the fact that the above problem has previously been solved by the subunit vaccines of the state of the art and that there is no evidence in the description that the nucleic or amino acid sequences SEQ ID NOs: 1 and 2 actually solve the problem through initiating an effective protective immune response to *Lawsonia intracellularis*, the subject-matter of claims 1 and 14 cannot be recognized as involving an inventive step according to Article 33(3) PCT.
- Dependent claims 10 to 13, 23 to 32, as far as they are dependent upon claims 1 and 14, do not appear to contain any additional features which, in combination with the features of any claim to which they refer, involve an inventive step.
- 3.6 In view of the above, the present application does not meet the requirements of Article 33(3) PCT, because the subject-matter of claims 1, 10 to 14, 23 to 32 does

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not involve an inventive step.

For the assessment of the present claims 23 and 24 on the question whether they are industrially applicable, no unified criteria exist in the PCT Contracting States. The patentability can also be dependent upon the formulation of the claims. The EPO, for example, does not recognize as industrially applicable the subject-matter of claims to the use of a compound in medical treatment, but may allow, however, claims to a known compound for first use in medical treatment and the use of such a compound for the manufacture of a medicament for a new medical treatment.